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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,726	BROWN ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/29/2005 and 11/02/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A and B*.

DETAILED ACTION

1. The examiner of the instant application has changed here at the Patent and Trademark office. Please direct future inquiries concerning this application to Brad Duffy whose telephone number is (571) 272-9935.

2. The election filed November 22, 2006, is acknowledged and has been entered.

Applicant has elected the invention of Group I with the specific combination of genes being NEK2, PLK1, ATR and CHEK1. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. The amendment filed November 22, 2006, is acknowledged and has been entered. Claims 1, 5 and 7 have been amended. Claims 2-4 and 8-20 have been canceled. Claims 21-25 are newly added.

4. Claims 1, 5-7 and 21-25 are pending and under examination in the application.

Election/Restrictions

5. Upon further consideration of the restriction and election requirement set forth in the Office action mailed May 26, 2006, the invention of Group I with the specific combination of genes being NEK2, PLK1, ATR and CHEK1 has been rejoined with inventions of Group I drawn to the genes being NEK2, PLK1, ATR and CHEK1 individually or in any combination. The restriction and election requirement separating these inventions has been withdrawn.

Information Disclosure Statement

6. The references, except for the Affymetrix manuals, cited in the information disclosure statements filed on March 29, 2005 and November 02, 2005 have been

considered. Since the Affymetrix manuals do not have a publication date listed, they were not considered (see MPEP 609). Additionally, while considered, the PCT search reports and the EMBL accession numbers are not published documents and therefore do not conform with the information disclosure statement requirements, so they were crossed out. (see MPEP 609). Furthermore, US Patents 5,151,254 and 5,919,619 were cited on both forms, so the second citation was crossed out. Applicant is requested to review the submitted IDSs to ensure that there are not any other duplicate citations.

Specification

7. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Gene Logic™ and BioExpress™; see, e.g., page 9, paragraph [0077].

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

(b) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

8. Claims 23-25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. These claims are not interpreted as a method of predicting whether a treatment regime would improve long-term prognosis because they ultimately depend from claim 1 which is drawn to a method of detecting a cancer marker, comprising detecting an expression profile of a least one gene selected from the group of NEK2, PLK1, ATR and CHEK1. Therefore, since the claims from which 23-25 depend are drawn to a process of detecting a cancer marker comprising detecting an expression profile, the further step of predicting whether a particular treatment regime would improve long-term prognosis in the human subject, does not properly limit the method of detecting a cancer marker, because the process steps outlined in detecting the expression profile are not limited by the "predicting" process step.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 5-7 and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1, 5-7 and 21-25 are indefinite because of the use of the terminology "NEK2, PLK1, ATR and CHEK1", as the sole means to identify genes in claim 1. The use of this terminology to identify the genes to which the claims are directed renders the claims indefinite because it fails to point out with the requisite particularity the identity of

the genes. Different laboratories often use the same nomenclature to identify distinct genes or use different nomenclature to identify the same gene. For example, the term "ATR" is used in the relevant art to identify at least three distinct genes, human ATR, xenopus ATR and the anthrax toxin receptor. (see attached Exhibit A that discloses the xenopus ATR gene and Exibit B that discloses the ATR as the anthrax toxin receptor). Accordingly, because it is unclear or cannot be ascertained what other genes are referred to as ATR, or what other nomenclature ATR might be known as in the art, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter. Furthermore, the specification on page 36 indicates that the invention encompasses not only the molecules described, such as the nucleic acids for the genes NEK2, PLK1, ATR and CHEK1, but also nucleic acids structurally different from the molecules described. Therefore, it is unclear which genes "NEK2, PLK1, ATR and CHEK1" refer to and the skilled artisan would not know or be able to determine infringing subject matter.

It is suggested that this issue be remedied by amending claim 1 to recite a limitation requiring that "NEK2, PLK1, ATR and CHEK1" each comprise a specific nucleic acid sequence respectively, which is disclosed in the specification, as filed, because such a limitation would serve to unambiguously identify the genes to which the claims are directed.

(b) Claims 1, 5-7 and 21-25 are indefinite because claim 1 is directed to a method for detecting a cancer marker; yet the claim merely recites the process of detecting the expression profile of one or more genes designated NEK2, PLK1, ATR and CHEK1 in a cancer tissue from a human subject. Are the NEK2, PLK1, ATR and CHEK1 genes individually "cancer markers" that are to be detected, are they detected as one "cancer marker" or is some other "cancer marker" detected? Since there is no process step that clearly relates back to the purpose or objective of the claimed invention the skilled artisan could not determine whether each and every process step considered essential to the practice of the claimed invention has been included in the body of the claim.

Thus, in the absence of a correlative step positively relating the whole of the process to its intended use, as recited in the preamble, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(c) Claim 5 recites the limitation "the biological sample" that is not present in claim 1. Therefore, there is insufficient antecedent basis for this limitation in the claim. In this case, claim 1 recites a cancer tissue, while the biological samples in claim 5 do not have to be cancer tissues.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 5-7 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed November 22, 2006 has introduced NEW MATTER into the claims. As amended, claim 1 recites the term "PLK1".

Applicant submits that the support for the amendment may be found throughout the specification, including the original claims, and at, for example, pages 9-11, 14-15, 18-19, 23 and 30-32,

However, upon reviewing the application, the term "PLK1" is not found in the originally filed specification. The specification describes a "PLK (Polo (Drosophia)-like kinase)" gene, which comprises the nucleic acid sequence of SEQ ID NO:31 (see page 11; and page 20, paragraph [0109]); but nowhere does the specification describe "PLK1".

Instant claims 1, 5-7 and 21-25 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in claims 1, 5-7 and 21-25, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112.

This issue might be remedied if Applicant were to point to specific disclosures in the specification, including the claims, as originally filed, which are believed to provide written support for the language of the claims.

13. Claims 1, 5-7 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: http://www.gpoaccess.gov/.

(a) In the instant case, claims 1, 5-7 and 21-25 are drawn to processes of detecting a broad genus of "cancer markers", comprising the step of detecting the expression

profile of the genes designated in the broad genus of "NEK2, ATR and CHEK1" alone or in any combination in a cancer tissue from a human subject.

In contrast to the breadth of the claims, the specification only describes detecting the nucleic acid sequences of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12, which according to Table 1 at pages 10 and 11 of the specification represent the genes designated "NEK2", "ATR" and "CHEK1", respectively, alone or in any combination, as markers of colon adenocarcinoma; and as noted above, the specification does not describe a cancer marker identified by the term "PLK1". Moreover, while the specification teaches that the nucleic acid sequences of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 are overexpressed in human colon adenocarcinoma cells, it also teaches that one or more of these sequences is *not* overexpressed in other types of cancers, such as lung, breast and prostate cancer (see pages 113-117, Table 6a).

The specification on page 33 describes that the presence of increased mRNA for any gene set forth in Table 1, or increased levels of the protein products of these genes serve as markers for cancer. Furthermore, the specification characterizes the genes NEK2, ATR and CHEK1 as represented by the nucleic acid sequences of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12, respectively on page 10 and 11 and describes on pages 9 and 10 that the mRNA of these genes are "upregulated in tissues from at least two of the four major types of cancers, i.e., colon adenocareinoma, lung adenocarcinoma, breast infiltrating ductal carcinoma, and prostate adenocarcinoma". The specification then provides a brief synopsis of these genes. For example, the specification states that "NEK2 may play a role in the regulation of centrosome separation", on page 19. However, on page 36 the specification characterizes the invention as encompassing polynucleotide molecules which are structurally different from molecules described (i.e., the genes NEK2, ATR or CHEK1), but have substantially the same properties as said molecules. Furthermore, the specification does not indicate what properties the molecules should share and the only property the specification definitively describes for the genes NEK2, ATR or CHEK1 is that they are overexpressed in colon adenocarcinomas. Thus, since the genes of the genus of "NEK2, ATR and CHEK1" are inclusive of structurally different molecules, it appears

that any gene that is overexpressed in colon adenocarcinomas is included in the "NEK2, ATR and CHEK1" genus.

Therefore, given the lack of particularity with which the genus of "cancer markers" or the genus of molecules encompassed by "NEK2, ATR and CHEK1" are described, it is submitted that the claims are directed to detecting any overexpressed mRNA or protein in a cancer cell. Bischoff et al (EMBO, 17(11):3052-3065, 1998), for example, describes that the aurora kinase 2 mRNA and protein is overexpressed in human colon adenocarcinoma cells (See entire document, e.g., page 3057, left column, figure 4, 5 and 6). Therefore, aurora kinase 2 is reasonably considered a member of the genus of "cancer markers" or the genus of "NEK2, ATR and CHEK1" to which the claims are directed because while aurora kinase 2 is structurally different than "NEK2, ATR and CHEK1", aurora kinase 2 shares the property of being overexpressed in colon adenocarcinomas like "NEK2, ATR and CHEK1", the only property of "NEK2, ATR and CHEK1" that is definitively described.

Accordingly, the genus of "cancer markers" and the genus of "NEK2, ATR and CHEK1" includes members, having substantially and significantly variant structures and/or functions. The specification fails to adequately describe this genus, as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other proteins, as the specification fails to describe its members as sharing any particularly identifying structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those genes because not all genes are overexpressed in all cancers.

In this case, "NEK2, ATR and CHEK1" would not be considered representative to one of skill in the art of "cancer markers" in general because not all the nucleic acids encompassed by the genes NEK2, ATR and CHEK1 are overexpressed in all cancers, i.e., even SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12, which are represented by the genes designated NEK2, ATR and CHEK1 respectively are not all overexpressed in breast, lung and prostate cancers. Furthermore, SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 would not be considered representative to one of skill in the art of the genus of "NEK2, ATR and CHEK1" because the disclosure encompasses in the genus

of "NEK2, ATR and CHEK1" nucleic acids that encode genes that are structurally and functionally unrelated to SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12.

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

(b) In the instant case, claims 23-25 recite methods comprising predicting whether a "particular treatment regime would improve long-term prognosis" and comprising targeting cancer cells overexpressing a gene in the genus of "NEK2, PLK1, ATR and CHEK1" with the broad genus of "siRNA or antibody" molecules.

In contrast to the breadth of the claims, the specification does not adequately describe any expression profiles of any genes that could be used to improve long-term prognosis. On page 85, the specification describes that "an expression pattern may

emerge to correlate a particular expression profile to increased likelihood of a poor prognosis." However, since the specification does not describe or correlate any particular expression profile with any prognosis, the skilled artisan would not understand that the Applicant had possession of the claimed invention at the time the application was filed.

Furthermore, as noted in the above written description rejection, since the specification does not have an adequate written description of the genus of "cancer markers" or the genus of "NEK2, PLK1, ATR and CHEK1", the broad genus encompassed by siRNAs or antibodies targeting "NEK2, PLK1, ATR and CHEK1" would also lack adequate written description.

14. Claims 1, 5-7 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method of detecting colon adenocarcinoma markers comprising detecting an expression profile of at least one nucleic acid in a colon cancer tissue from a human subject, wherein said at least one nucleic acid is selected from the group of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12, wherein said at least one nucleic acid is overexpressed compared to a normal colon tissue reference control, **and while being enabling for using** any process encompassed by the claims, which has been described by the prior art, **does not reasonably provide enablement for using** the claimed processes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Applicant is reminded reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

While the specification indicates that the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 are overexpressed in colon cancer tissues from human subjects compared to normal colon tissues.

Thus, the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 would not be considered "markers" of colon adenocarcinomas.

However, the specification also teaches that the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 are *not* overexpressed in all cancers (see page 105 and table 6a that indicates qualifiers 37229_at, which corresponds to SEQ ID NO:1, 38920_at, which corresponds to SEQ ID NO: 12, 37228_at, which corresponds to SEQ ID NO:31 and 366_s_at, which corresponds to SEQ ID NO:26 are not overexpressed in at least one other type of cancer).

Thus, the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 would not be considered "markers" of all types of cancer, but rather only markers of colon adenocarcinomas.

The skilled artisan cannot predict whether the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 are overexpressed in any type of cancer other than colon adenocarcinoma; and given the unpredicatability of expression of SEQ ID NO:26, SEQ ID NO:1 and SEQ ID NO: 12 in lung, breast and prostate cancers, the specification would not reasonably enable the skilled artisan to use the claimed process for identifying a "cancer marker" because undue and/or unreasonable experimentation would be required to determine if the expression profile of one or more of the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12, together or in any combination, characteristically identifies a particular type of cancer.

Furthermore, even while the nucleic acids of SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 are overexpressed in colon adenocarcinoma tissues, it is submitted the artisan cannot predict whether *the protein* encoded by SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 is also overexpressed in this, or any type of cancer.

This position is supported, for example, by the teachings of Lichtinghagen et al (European Urology (42):298-406, 2002) and Chen et al (*Mol. Cell. Proteomics.* 2002 Apr; 1 (4): 304-313). Lichtinghagen et al. teach that while the mRNA levels of MMP-9 and TIMP-1 where unchanged in prostate tumor tissues, the protein level of MMP-9 was higher and the protein level of TIMP1 was lower in tumor tissue when compared to normal tissue (see entire document, e.g., page 400). Additionally, Chen et al. teach that expression of protein and the mRNA encoding said protein are discordant in cancer (see entire document e.g., the abstract). Consequently, it is unpredictable whether the

proteins encoded by SEQ ID NO:26, SEQ ID NO:1, and SEQ ID NO: 12 are also overexpressed in colon adenocarcinoma or other cancer tissue.

Furthermore, since the claims are directed to an inadequately described genus of genes identified by the terms "NEK2", "PLK1", etc., which are interpreted to include, for example, a gene encoding *Xenopus* "ATR", (see page 36 of the specification that characterizes the invention as inclusive of homologs of genes from other species) which is not expressed in human tissues and would not serve to identify a "cancer marker" according to the claimed process. In light the unpredictability of the genes being overexpressed in a particular cancer and a lack of working examples of homologs from other species being expressed in human tissue, it is submitted that the skilled artisan would not know how to detect all of the genes encompassed by the claims as "cancer markers" in human tissue.

Additionally, since claims 23-25 do not properly limit the claims from which they depend they are drawn to a method of detecting a cancer marker further comprising predicting whether a particular treatment regime would improve long-term prognosis and wherein the treatment regime comprises targeting said at least one gene with an siRNA or antibody lack enablement because the specification provides no guidance, direction or exemplification as to how a method of detecting a cancer profile would be indicative of any particular treatment regime and provides no guidance, direction or exemplification as to which siRNA or antibody treatment would be indicated by a particular expression profile. Since there is no correlation between any cancer marker and any treatment (either an art recognized treatment or a novel treatment) targeting the genes of the invention, the skilled artisan would be subject to undue experimentation to determine if a given detecting a particular cancer profile was indicative of a particular treatment and/or if a novel treatment was effective in improving the long-term prognosis in a human. It has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap (Chatterjee et al., Cancer Immunology and Immunotherapy, 38:75-82, 1994). Therefore, the amount of guidance, direction and exemplification set forth in the specification is not reasonably commensurate in scope with the breadth of

the claims. Unless detecting a particular cancer marker correlates with a long-term prognosis that indicates a known treatment regime, it is submitted that the skilled artisan could not reasonably use a cancer marker to determine which treatment regime would be indicated to improve long-term prognosis.

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify cancer markers that correlate with a particular prognosis and test treatment regimes to see if they would improve a patient's prognosis.

For these reasons, the specification does not enable predicting whether a particular treatment regime would improve long-term prognosis, nor whether targeting a particular gene of the invention would be an effective treatment.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1, 5-7 and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Bischoff et al (EMBO, 17(11):3052-3065).

The claims are herein drawn to of detecting a colon adenocarcimona marker comprising determining the expression profile of at least one gene in a colon adenocarcimona tissue and comparing said expression profile to a reference expression profile from a normal colon sample using an immunoassay, wherein at least one gene is overexpressed in said cancer tissue.

Support for this interpretation occurs in the specification where it characterizes that the invention as encompasses polynucleotide molecules which are structurally different from the molecules described, but have substantially the same properties as said molecules. (underlining added for emphasis) (see specification page 36). However, the specification in unclear what "substantially the same properties" the genes of the invention are required to have and only definitively describes that the NEK2, ATR and CHEK1 genes are all overexpressed in colon adenocarcinoma tissue. Therefore the genus of "NEK2, ATR and CHEK1" is interpreted as including any gene that is overexpressed in colon adenocarcinoma tissue.

Bischoff et al teach detecting the aurora kinase 2 protein expression profile by immunoassay in primary human adenocarcinoma tissue samples and comparing said expression profile to the expression profile of cancer-free colon tissue. (see entire document, e.g., page 3058, right column and Figure 6). Bischoff et al also teach that the aurora kinase 2 protein is overexpressed in primary human adenocarcinoma tissue samples compared to normal samples (e.g., page 3058, right column and Figure 6).

In this case, the aurora kinase 2 protein of the prior art is materially and structurally indistinguishable from the genes encompassed by the genus of NEK2, ATR and CHEK1 to which the claims are directed. Therefore, absent a showing of any difference, the claimed process and the process disclosed by the prior art are deemed the same.

17. Claims 1, 5-7 and 21-22 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2004/0063108 (Mack et al, published April 1, 2004).

The claims are herein drawn to of detecting a colon adenocarcimona marker comprising determining the expression profile of at least one gene in a colon adenocarcimona tissue by RT-PCR, microarray or immunoassay and comparing said expression profile to a reference expression profile from a normal colon sample, wherein at least one gene is overexpressed in said cancer tissue.

Support for this interpretation occurs in the specification where it characterizes that the invention as encompasses polynucleotide molecules which are structurally different from the molecules described, but have substantially the same properties as said molecules. (underlining added for emphasis) (see specification page 36). However, the specification in unclear what "substantially the same properties" the genes of the invention are required to have and only definitively describes that the NEK2, ATR and CHEK1 genes are all overexpressed in colon adenocarcinoma tissue. Therefore the genus of "NEK2, ATR and CHEK1" is interpreted as including any gene that is overexpressed in colon adenocarcinoma tissue.

Mack et al teach the expression profiles of 93 genes that are overexpressed in colon adenocarcinoma compared to a normal colon sample (see entire document, e.g., page 33, table 1). Mack et al also teach that detecting the levels of these 93 genes by RT-PCR, microarray or immunoassay. (e.g., page 20, right column and page 21, left column).

In this case, the 93 genes of the prior art are materially and structurally indistinguishable from the genes encompassed by the genus of NEK2, ATR and CHEK1 to which the claims are directed. Therefore, absent a showing of any difference, the claimed process and the process disclosed by the prior art are deemed the same.

18. Claims 1, 5-7 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 2002/068579 (Venter et al, published September 6, 2002).

The claims are herein drawn to a method comprising determining the expression profile of at least one gene in a breast, colon or lung cancer tissue by RT-PCR or microarray wherein the genes are selected from NEK2, ATR and CHEK1 and comparing said expression profile to a reference expression profile from a normal breast, colon or lung sample.

Venter et al teach 39,010 nucleic acids that correspond to the genes of the annotated human genome and the detection of expression profiles of at least one of the said nucleic acids by microarray or RT-PCR (see entire document, e.g., page 3, page 8, page 20 and page 24. Venter et al also teach comparing said expression profiles from cancerous tissues to expression profiles from normal tissue samples from breast, colon or lung tissues (e.g., page 5 and page 28). While, Venter et al do not expressly teach the names of the genes as NEK2, ATR or CHEK1, Venter inherently teaches genes that are materially and structurally indistinguishable from the claimed genes as they teach the genes corresponding to the human genome, which inherently includes genes named NEK2, ATR and CHEK1.

Therefore, absent a showing of any difference, the claimed process and the process disclosed by the prior art are deemed the same.

19. Claims 1, 21 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Wai et al., (Int J Oncol., 20(3):441-51, March 2002).

The claims are herein drawn to a method comprising determining the expression profile of NEK2 in a cancer tissue by microarray and comparing said expression profile to a reference expression profile, wherein NEK2 is overexpressed in the cancer tissue.

Wai et al that NEK2 is overexpressed in cell lines originating from Ewing tumors (ETs) (malignant primary bone tumors) compared to reference cell lines, NB and GG-62 (see entire document, e.g., page 441, 446 and figure 2A).

Therefore, Wai et al anticipate these claims.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1, 5-7 and 21-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-8 of copending Application No. 10/751,736. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are described supra.

Claims 7-8 of copending Application No. 10/751,736 are drawn to a method comprising detecting an expression profile of one or more colon cancer genes in a biological sample and comparing said expression profile to a control expression profile of said one or more genes, wherein one or more colon cancer genes are differentially expressed and the genes comprise at least one gene selected from Tables 1-5.

Support for this interpretation occurs in the specification where it characterizes that the invention as encompasses polynucleotide molecules which are structurally

different from the molecules described, but have substantially the same properties as said molecules. (underlining added for emphasis) (see specification page 36). However, the specification in unclear what "substantially the same properties" the genes of the invention are required to have and only definitively describes that the NEK2, ATR and CHEK1 genes are all overexpressed in colon adenocarcinoma tissue. Therefore the genus of "NEK2, ATR and CHEK1" is interpreted as including any gene that is overexpressed in colon adenocarcinoma tissue.

It is noted the specification discloses that the genes in Tables 1-5 are overexpressed in colon cancer compared to normal tissue (see page 11 of 751,736).

In this case, the genes listed in Tables 1-5 are materially and structurally indistinguishable from the genes encompassed by the genus of NEK2, ATR and CHEK1 to which the claims are directed. Therefore, absent a showing of any difference, the claimed process and the process disclosed by copending Application No. 10/751,736 are deemed the same.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

Conclusion

22. No claims are allowed.

23. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Holtrich et al (PNAS, (91):1736-1740) teach detecting the mRNA expression profile of PLK in colon adenocarcimona tissues.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

STEPHEN L. RAWLINGS, PH.D.
PRIMARY EXAMINER

☐ 1: AAG34794. Reports Atr protein [Xeno...[gi:11385422]

BLink, Conserved Domains, Links

Features Sequence

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VERSION     AAG34794.1  GI:11385422
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            in Xenopus egg extracts
  JOURNAL   Genes Dev. 14 (21), 2745-2756 (2000)
   PUBMED   11069891
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  AUTHORS   Guo,Z., Kumagai,A. and Dunphy,W.G.
  TITLE     Direct Submission
  JOURNAL   Submitted (11-JAN-2000) Division of Biology 216-76, California
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1: Sheng Wu Gong Cheng Xue Bao. 2005 Sep;21(5):826-31.

[Expression of ATR-Fc fusion protein in CHO cells]

[Article in Chinese]

Gao LH, **Hu XW**, **Chen W**, **Xu JJ**, **Zhao J**, **Chen HP**.

Beijing Institute of Biotechnology, Beijing 100071, China.

ATR-Fc is a fusion protein consisting of extracellular domain of human anthrax toxin receptor (ATR) and a fragment (hinge, CH2, and CH3 domains) of the Fc of human IgG1. The aim of ATR-Fc expression is to get an antibody-like molecule binding to protective antigen (PA), a component of anthrax toxins, this fusion protein may compete with cell surface receptor for PA binding, and block the transport of lethal factor (LF) and edema factor (EF) into cells, thereby act as an antitoxin to prevent and treat anthrax infection. A DNA fragment encoding N-terminal amino acids 1-227 of ATR and human IgG1 Fc was inserted into the Hind III and Not I sites of pcDNA3.1 to generate the eukaryotic vector pcDNA3.1/ATR-Fc for expression of ATR-Fc fusion protein. Using lipofectine-mediated gene transfer technique, pcDNA3.1/ATR-Fc was transfected into CHO-K1 cells. After selected with G418, a recombinant CHO cell line, ATR-Fc-1D5, whose expression level was about 10 - 15 microg/(10(6) cells x d), was established. The recombinant protein expressed by the ATR-Fc-1D5 cells was purified with protein A chromatography. The experimental results demonstrated a direct and specific interaction between ATR-Fc and PA assessed by ELISA.

PMID: 16285529 [PubMed - in process]